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**14. ABSTRACT**
The objectives are to 1) elucidate the pathogenesis of ovarian cancer by characterizing the early lesions, and 2) to provide biomarkers for early ovarian cancer detection. Both goals will be facilitated by this Consortium Development plan which is a collaborative, interdisciplinary program that will establish the infrastructure to coordinate research. The research sites include Johns Hopkins University, Toronto University, Memorial Sloan Kettering Cancer Center, and Yale University. The Coordination center will have three Cores. The specific goals to be accomplished are briefly summarized. The Administrative Core will collect IRB protocols from all research sites, organize the Consortium symposium including the Pathology/Epidemiology consensus meeting, setup and test the audio-video broad band electronic device for e-conference, organize the Internal Advisory Board. The Pathology/Epidemiology Core will define criteria for early ovarian cancer lesions and select cases/controls, survey available cases and controls from all research sites, create one overall database for specimens with clinical and epidemiologic data, establish tissue trafficking mechanisms. The Biostatistics Core will establish the data collection, storage and security system, and perform statistics support in study design. The completion of these tasks is considered critical for us to continue our research in the coming Consortium research program.

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Ovarian cancer, cauterization, development, molecular.

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**Introduction**

The purpose of the Consortium are to **1)** elucidate the pathogenesis of ovarian cancer by characterizing the early lesions involved in the development of high-grade ovarian serous carcinoma, and **2)** to provide biomarkers for early ovarian cancer detection. Both goals will be facilitated by this Consortium Development plan which is a collaborative, interdisciplinary program that will establish the infrastructure to coordinate basic and translational research. Thus, the main purpose of the proposed Consortium Development project is to establish the infrastructure for supporting the future Consortium research program focusing on identification and characterization of early molecular changes in ovarian cancer. The consortium is composed of four research sites and one Coordination center. The four research sites include Johns Hopkins University (JHU), Toronto University Health Network (TUHN), Memorial Sloan Kettering Cancer Center (MSKCC), and Yale University. The Coordination center will have three Cores (Administration, Biostatistics, and Pathology/Epidemiology) which will provide the essential support and integration of the projects from the research sites. JHU will be the Coordinating center with purview over the three Cores which in turn will coordinate the activities of the four research sites.

Dr. Kurman is the Director of the proposed Consortium development and will oversee the program. Dr. Kurman is currently the Director of Gynecologic Pathology at the Johns Hopkins Medical Institutions and has had a specific interest in gynecologic pathology for over 30 years.  Dr. Kurman is a national and internationally recognized authority in the field of ovarian pathology and has published extensively on all types of ovarian neoplasms. Under the leadership of Dr. Kurman, the individual projects will act in a synergistic and highly integrated fashion aimed at better understanding the molecular landscape of early/precursor lesions of ovarian cancer in the future consortium program project.

The scope of the Development award is briefly summarized. The Administrative Core will collect IRB protocols from all research sites, organize the Consortium symposium including the Pathology/ Epidemiology consensus meeting, setup and test the audio-video broad band electronic device for e-conference, organize the Internal Advisory Board, assemble research protocols for shared techniques.  The Pathology/Epidemiology Core will define criteria for early ovarian cancer lesions (precursors) and select cases and controls, survey available cases and controls from all research sites, create one overall database for specimens with clinical and epidemiologic data, establish tissue processing and trafficking mechanisms, setup quality control procedures for DNA, RNA and protein extraction. The Biostatistics Core will establish the data collection, storage and security system, perform power calculation, sample size justification and participate in study design for each project. Each research site will establish regular research conferences, formulate research specific aims, identify expert collaborators and consultants, and collaborate with Pathology/Epidemiology Core to identify pre-existing early lesions and precursors. The completion of these tasks is considered critical for us to continue our research in the future Consortium research program.

**Body**

We have brought expertise of pathology, epidemiology, molecular techniques and tissue banking to focus on studying the pathogenesis of ovarian cancer development. The main tasks (according to the Statement of Work as originally submitted) that have been accomplished in this Development phase are followings.  **First**, we have successfully brought together several institutions including Johns Hopkins University (JHU), Toronto University Health Network (TUHN), Memorial Sloan Kettering Cancer Center (MSKCC), and Yale University with clinics of women at high risk of developing ovarian cancer.  We have set up a collaboration network of

investigators at these institutions who have had a long-term interest in ovarian tumorigenesis, particularly in the characterization of molecular events related to the development of early lesions and their early detection. **Second**, we are creating a Coordination center to facilitate the interaction, integration and cohesion of this program. This goal has been achieved by establishing three Consortium Cores (Administration, Biostatistics, and Pathology/ Epidemiology). **Third**, we have set up different levels of communication to facilitate the interactions among investigators. **Finally**, we are inviting clinicians and patients to be active participants in this Consortium and they will work with the scientists to provide clinical insights into research projects. The details of progress are summarized in Table 1. We are fortunate that our consortium has been selected as the Consortium award in 2011. We have requested the "no-cost-extension" which has been granted by US AMRMC for another year to continue the tasks related to consortium development such as support for the incoming Ovarian Cancer Symposium and purchase of containers for slides and tissue blocks, etc.

Table 1. Tasks proposed in the Development phase and the status of accomplishment.

| Tasks proposed | Accomplished |
|---|---|
| Administration Core (JHU) | • Organize the Consortium symposium including the Pathology/Epidemiology consensus meeting; <br> • Setup and test the audio-video broad band electronic device for e-conferences; <br> • Organize the Internal Advisory Board; |
| Pathology and Epidemiology Core (JHU) | • Define criteria for early ovarian cancer lesions (precursors) and select cases and controls through the consensus meeting; <br> • Survey available cases and controls from all research sites; <br> • Establish tissue processing and trafficking mechanisms; <br> • Set up quality control procedures for DNA, RNA and protein extraction |
| Biostatistics Core (JHU) | • Establish the data collection, storage and security systems; <br> • Perform power calculation and sample size justification for each project; <br> • Participate in study design of individual projects |
| Research sites (JHU, TUHN, MSKCC, Yale) | • Establish regular research conferences at each site; <br> • Formulate research specific aims; <br> • Identify expert collaborators and consultants; <br> • Collaborate with Pathology/Epidemiology Core to identify pre-existing early lesions and precursors; <br> • Investigators have attended the DoD pre-award meeting at Fredrick |

**Key Research Accomplishments**

This is a Development award, and organization and coordination rather than research are the main focus of this project. Nevertheless, the investigators have taken advantage of the Development award to work together for a project aiming at defining the diagnostic criteria of the ovarian precursor lesions in the fallopian tubes. This study has been peer-reviewed and accepted for publication in *American Journal of Surgical Pathology*.

Moreover, the consortium investigators have also published several papers related to the studies of early ovarian cancer lesions (please see appendices for details).

**Reportable Outcomes**

- The Consortium Development award has built up the necessary infrastructure to mature into a full Consortium program project which focuses on characterizing the early ovarian cancer lesions and precursors.

- This consortium has been selected for the second phase Ovarian Cancer Consortium award.

- As stated in the application, we have established the website for researchers and patients: http://www.ovariancancerprevention.org/

- Publication from the Development award: Visvanathan K, Vang R, Shaw P, Gross A, Soslow R, Parkash V, Shih IM, Kurman RJ. Diagnosis of serous tubal intraepithelial carcinoma (STIC) based on morphologic and immunohistochemical features- a reproducibility study. Am J Surg Pathol, in press. *Please see Appendices for other publications.*

- We have negotiated with the Department of Pathology at the Johns Hopkins University School of Medicine and acquire an additional research bay designated for the Consortium projects and Pathology Core (Figure 1). It is located at CRB-2 (Cancer Research Bldg) in the medical campus, adjacent to Drs. Shih and Wang (co-investigators) pre-existing research areas (see picture below).



**Figure 1.** The new space allocated for the DoD Consortium project research. This bay has two benches, located in CRB-2 at the medical campus of Johns Hopkins Medical Institutions. We plan to use this space for Pathology Core and Project 1 and Project 4 in the Consortium program.

**Conclusion**

The Consortium Development award has provided us the ground that is necessary to assembly a highly productive team consisting of many enthusiastic researchers from different initiations for ovarian cancer research. This can be only made possible through this DoD Development grant mechanism which turns out to be highly effective and rewarding. The major tasks as proposed have been completed and the infrastructure established would greatly facilitate our future Consortium phase containing 5 research projects and 3 centralized cores. All the participating investigators and collaborators appreciate this opportunity to continue their

collaboration are looking forward to the next phase of research endeavor and challenge to elucidate the pathogenesis of ovarian cancer from the perspective of studying early and precursor lesions.

**References**

None.

**Appendices**

**Appendices- publications and abstracts generated by the investigators in this Consortium**

Am J Surg Pathol. 2010 Mar;34(3):433-43.
**The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory.**
Kurman RJ, Shih IeM.
http://www.ncbi.nlm.nih.gov/pubmed/20154587

Am J Surg Pathol. 2010 Oct;34(10):1407-16.
**Are all pelvic (nonuterine) serous carcinomas of tubal origin?**
Przybycin CG, Kurman RJ, Ronnett BM, Shih IeM, Vang R.
http://www.ncbi.nlm.nih.gov/pubmed/20861711

Am J Surg Pathol. 2010 Jun;34(6):829-36.
**Shortened telomeres in serous tubal intraepithelial carcinoma: an early event in ovarian high-grade serous carcinogenesis.**
Kuhn E, Meeker A, Wang TL, Sehdev AS, Kurman RJ, Shih IeM.
http://www.ncbi.nlm.nih.gov/pubmed/20431479

J Oncol. 2010;2010:126295. Epub 2010 Apr 27.
**Precursor lesions of high-grade serous ovarian carcinoma: morphological and molecular characteristics.**
Gross AL, Kurman RJ, Vang R, Shih IeM, Visvanathan K.
http://www.ncbi.nlm.nih.gov/pubmed/20445756

Gynecol Oncol. 2010 Sep;118(3):295-8.
**Risk factors for non-invasive lesions of the fallopian tube in BRCA mutation carriers.**
Vicus D, Shaw PA, Finch A, Rosen B, Murphy J, Armel S, Sun P, Narod SA.
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Toronto, Ontario, Canada.
http://www.ncbi.nlm.nih.gov/pubmed/20722102

Mod Pathol. 2010 Jun;23(6):844-55. Epub 2010 Mar 12.
**Serous tubal intraepithelial carcinoma upregulates markers associated with high-grade serous carcinomas including Rsf-1 (HBXAP), cyclin E and fatty acid synthase.**
Sehdev AS, Kurman RJ, Kuhn E, Shih IeM.
http://www.ncbi.nlm.nih.gov/pubmed/20228782

Future Oncol. 2009 Dec;5(10):1641-57.
**Pathogenesis of ovarian cancer: clues from selected overexpressed genes.**
Shih IeM, Davidson B.
http://www.ncbi.nlm.nih.gov/pubmed/20001801

Cancer Res. 2009 May 1;69(9):4036-42. Epub 2009 Apr 21.
**Analysis of DNA copy number alterations in ovarian serous tumors identifies new molecular genetic changes in low-grade and high-grade carcinomas.**
Kuo KT, Guan B, Feng Y, Mao TL, Chen X, Jinawath N, Wang Y, Kurman RJ, Shih IeM, Wang TL.
http://www.ncbi.nlm.nih.gov/pubmed/19383911

Am J Obstet Gynecol. 2008 Apr;198(4):351-6.
**Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis.**
Kurman RJ, Visvanathan K, Roden R, Wu TC, Shih IeM.
http://www.ncbi.nlm.nih.gov/pubmed/18395030

Clin Cancer Res. 2008 Jul 1;14(13):4067-78.
**Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high-grade serous carcinoma.**
Tone AA, Begley H, Sharma M, Murphy J, Rosen B, Brown TJ, Shaw PA.
http://www.ncbi.nlm.nih.gov/pubmed/18593983

**Relevant Abstracts submitted to the annual meeting of**
**Unites States and Canadian Academy of Pathologists**
**(USCAP), San Antonio, Texas, 2011**

**Abstract-1**
*TP53* **mutations in serous tubal intraepithelial carcinoma and**
**concurrent ovarian high-grade serous carcinoma**

Elisabetta Kuhn1, Robert Kurman1, Robert Soslow2, Guangming Han2, Tian-Li Wang1 and Ie-Ming Shih1.
1Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, United States and 2Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States.

**Background:** Somatic mutation of *TP53* is the most common molecular genetic alteration in high grade serous carcinoma (HGSC) of the ovary, occurring in more than 95% of cases. As serous tubal intraepithelial carcinomas (STICs) have been proposed to be the most likely precursor of HGSC, we undertook a study to determine whether STICs harbor *TP53* mutations as well. Mutations of *TP53* have been reported in STICs and associated HGSC but that study [1] was limited to 5 cases. We therefore performed *TP53* mutational analysis in a larger series of STICs and concurrent HGSCs and correlated the mutational status with p53 immunoreactivity.
**Design:** Formalin-fixed paraffin-embedded tissue specimens were obtained from 18 HGSCs with concurrent STICs; 8 of them contained two discrete STICs. Approximately 1,000 cells from STIC and normal-appearing fallopian tubal epithelium were laser-capture microdissected from STICs, while HGSCs were manually microdissected. Genomic DNA was extracted, PCR amplified and sequenced. *TP53* mutations were analyzed from exons 4 to 8. Immunohistochemistry (IHC) for p53 was performed in all the cases.
**Result:** *TP53* mutations were detected in 15 (83.3%) of 18 HGSCs. Importantly, *TP53* mutations were not detected in the corresponding FTE samples from the same patients, confirming they are somatic mutations in HGSCs. STIC and associated HGSC shared identical *TP53* mutations in 15 (93.8%) of 16 patients including 7 who had two STICs. The discordant case showed *TP53* mutation in the HGSC but not in two separate concurrent STICs. By IHC, all the cases demonstrated the same pattern of p53 immunoreactivity (either all positive or completely

negative) except the case with wild-type *TP53* in the STIC and mutant *TP53* in the HGSC. By IHC the STIC was p53 negative and the HGSC p53 positive. The three *TP53* wild-type HGSCs and their associated STICs exhibited undetectable nuclear p53 by IHC. In contrast, four p53-negative HGSCs contained mutant *TP53* with either a deletion or an insertion mutation.

**Conclusion:** Our findings provide cogent evidence that *TP53* mutations occur in most STICs, and that both STIC and concurrent HGSC share the identical *TP53* mutations in the majority of cases. Future molecular genetic studies are necessary to delineate the clonal relationship and tumor progression from STIC to HGSC.

**Abstract-2**

**The diagnostic and biological implications of laminin expression in serous tubal intraepithelial carcinoma**

Elisabetta Kuhn1, Robert Kurman1, Robert Soslow2, Guangming Han2 and Ie-Ming Shih1
1Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, United States and 2Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States.

**Background:** Mounting evidence indicates that serous tubal intraepithelial carcinoma (STIC) is the likely precursor of most ovarian high-grade serous carcinomas (HGSCs). It has been proposed that cells from STICs are shed from the fallopian tube and implant on the ovary developing into a tumor, which simulates a primary HGSC. However, the molecular mechanisms underlying the dissemination of the cells from a STIC are not known. In order to identify the molecules that may be responsible for this critical process, we analyzed the ovarian cancer gene expression and identified several upregulated genes associated with HGSC. Among these, we selected laminin for further study because it has been shown to be involved in cell adhesion, motility and invasion.

**Design:** RT-PCR was used to assess the expression of different laminin isoforms (LAMA2, LAMA3, LAMC1, and LAMC2) in fresh tissue samples from 8 ovarian HGSCs, 9 ovarian cancer cell lines and 12 primary cultures of normal fallopian tube epithelium (FTE). Immunohistochemistry for LAMA3, LAMC1, p53 and Ki-67 was performed on formalin-fixed paraffin embedded tissue sections from 18 STICs, 16 of which were associated with concurrent ovarian HGSCs. LAMA3 and LAMC1 were scored based on intensity of cytoplasm (0 to 3+), and p53 and ki67 based on percentage of positive cells.

**Result:** RT-PCR, showed a statistically significant increase of LAMA2 ($p=0.044$) and LAMC1 ($p=0.0006$), and reduction of LAMA3 ($p=0.0032$) and LAMC2 ($p=0.0006$) in the HGSCs samples and the ovarian cancer cell lines as compared to controls. LAMA3 was expressed in normal FTE, STICs and HGSCs and was decreased in intensity in 9 (56%) of 16 HGSCs compared to STICs and FTE. Intense LAMC1 immunoreactivity (2+ and 3+) was detected in 17 (94.4%) of 18 STICs and 14 (87.5%) of 16 of the concurrent HGSCs whereas the LAMC1 staining was undetectable or weak (1+) in all FTE from the same patients. Interestingly, LAMC1 immunoreactivity was intense in 7 STICs in which p53 staining was absent and in 5 STICs with low Ki-67 index (<20%).

**Conclusion:** LAMC1 appears to play an important role in the development of HGSC. Since it is involved in cell adhesion, motility and invasion, upregulation of LAMC1 may facilitate shedding and dissemination of STIC cells to the ovaries and other peritoneal and abdominal structures. The presence of LAMC1 immunoreactivity in STICs, especially those with negative p53 staining and low Ki-67 labeling index, suggests that LAMC1 could be a reliable tissue biomarker to identify STICs.

**Abstract-3**

**Interobserver diagnostic concordance of serous tubal intraepithelial carcinoma and related lesions**

Russell Vang1, Kala Visvanathan2, Vinita Parkash3, Patricia Shaw4, Ie-Ming Shih1, Amy Gross2, Robert Soslow5 and Robert Kurman1.
1Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, United States; 2Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States; Pathology, Yale University School of Medicine3; Pathology, University of Toronto, Toronto, Canada4

**Introduction:** Serous tubal intraepithelial carcinoma (STIC) is a candidate precursor to pelvic high grade serous carcinoma (HGSC). There also exists a spectrum of lesions that are putative STIC precursors, namely "p53 signature," which lacks nuclear atypia, and tubal intraepithelial lesion in transition (TILT), which exhibits atypia, but falls short of STIC. A recent study (Carlson, et al.) reported suboptimal interobserver concordance when morphologic guidelines, but not immunohistochemistry (IHC), were used for categorization. The current study tested an algorithm to enhance interobserver concordance, with the ultimate goal of developing a classification scheme that can be used for diagnostic standardization.
**Methods:** Empirically derived morphologic criteria were tested using a panel of 6 pathologists who independently examined 67 lesions in round 1. An around-the-scope training session and IHC (using p53 and Ki-67) were added to morphologic examination, followed by independent assessment of 42 cases in round 2.
Round 2. STIC: serous tubal intraepithelial carcinoma; STIL: serous tubal intraepithelial lesion
**Results:** From round 1 to 2, kappa values improved from 0.3 to 0.5 for normal/reactive lesions, from 0.1 to 0.35 for atypical/p53 signature/STIL [akin to TILT], and from 0.4 to 0.78 for STIC.
**Conclusions:** Very good-to-excellent concordance was achieved for categorizing STIC using a combination of morphologic assessment and IHC. Further work is required to optimize reproducibility for lesions falling short of STIC.

**Abstract-4**

**Proliferative activity in serous tubal intraepithelial carcinoma compare to adjacent normal tubal epithelium and concurrent high-grade serous carcinoma**

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**Background:** Serous tubal intraepithelial carcinoma (STIC) has been recently recognized as a potential precursor lesion of ovarian high-grade serous carcinoma (HGSC) but reproducibly diagnosing it, even among expert gynecologic pathologists, can be very difficult. Although proliferative activity as indicated by the Ki-67 labeling index has been reported to be increased in STICs, a direct comparison of the Ki-67 index in the STIC to normal-appearing fallopian tubal epithelium (FTE) and the associated ovarian HGSC in the same patient has not been described. In this study we compare the Ki-67 index of FTE, STIC and ovarian HGSC in the same patient to evaluate whether Ki-67 staining can assist in the diagnosis of a STIC.
**Design:** A total of 33 STICs were analyzed, and among them 29 were associated with concurrent HGSC. Nine normal fallopian tubes from postmenopausal patients without neoplastic diseases were included as controls. Histological diagnosis of STICs was made according to previously reported morphological criteria (1). The Ki-67 index (using the Mib-1 antibody) was determined by calculating the percentage of cells showing nuclear immunoreactivity, in three random 20X-power fields. A minimum of 250 cells was counted.
**Result:** Immunoreactivity for Ki-67 in FTE was restricted to a few scattered cells and no statistically significant difference was found between patients with and without HGSC (p>0.05). On the other hand, both STICs and HGSCs had significantly higher Ki-67 indices than normal FTE (p< 0.0001). STICs were uniformly positive for Ki-67, with an index raging between 11.7%-71.1%. Ki-67 immunoreactivity was predominantly located in the basal layer in STICs. Based on the findings in 42 FTE specimens, we propose to use the mean Ki-67 index (2.4%) + 3 standard deviations (2.8% x 3) which approximated 10% as the cutoff to distinguish STICs (including p53 negative ones) from normal FTE (100% sensitivity and 93% specificity). In 29 cases with concurrent ovarian HGSC, the Ki-67 labeling index was higher in STIC vs. HGSC in 12/29 (41.4%) while it was lower in 17/29 (58.6%) (p=0.55).
**Conclusion:** Our data indicate that STICs have a high Ki-67 index similar to HGSC and that a Ki-67 >10% is a useful adjunct in making the diagnosis.